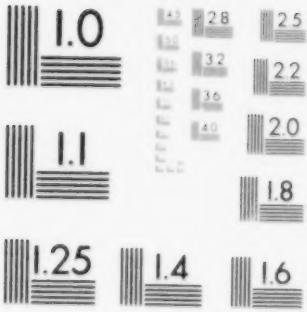


MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

Health Canada Santé Canada

Canada

# Canadian Adverse Reaction Newsletter

Volume 12 • Issue 3 • July 2002

www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html

## In this Issue

Pure red cell aplasia and Eprex 1
Glitazones: update on adverse reactions 2
Safety of human insulins 3
Case presentation: Kava 3
Summary of advisories 4

## Scope

**This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.**

## Reporting Adverse Reactions

**Contact Health Canada or a Regional AR Centre free of charge**

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

**Form available at:**

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

## Pure red cell aplasia: suspected association with epoetin alfa (Eprex)

Eprex, a recombinant human erythropoietin (rHuEPO), is indicated for "the treatment of anaemia associated with chronic renal failure (CRF), cancer or concomitantly administered cancer chemotherapy, zidovudine-treated/HIV-infected patients, for use in patients undergoing autologous donation, and to reduce allogenic blood exposure for patients undergoing elective surgery."[1] The "primary adverse effect of erythropoietin has been an excessive increase in the hematocrit following over-treatment with the hormone in patients undergoing hemodialysis, leading to the aggravation of hypertension or thrombotic complications."[2] Recently, however, pure red-cell aplasia (PRCA), a selective failure of the erythroid elements in bone marrow resulting in a normochromic, normocytic anemia, has been reported to be associated with the use of rHuEPO.[3-5] On Nov. 26, 2001, following discussion with Health Canada, the sponsor issued a Dear Healthcare Professional Letter informing physicians of the occurrence of PRCA associated with the use of Eprex.[6] Since then, there has been a marked increase in the number of PRCA cases reported to Health Canada: 21 of the 28 cases reported as of Apr. 10, 2002, were received after the letter was issued.

The mechanism underlying PRCA is not well understood. Autoantibodies against erythropoietin have been shown to inhibit the formation of erythroid colonies by normal bone marrow cells.[5] PRCA has been demonstrated to be induced by drugs and chemicals (e.g., phenytoin, chlorpropamide).[2,5,7] It has also been associated with a variety of conditions including thymomas, lymphoproliferative disorders and viral infections such as hepatitis B and parvovirus infection.[2,7] Although rare, PRCA can occur during the course of renal failure.[2,7] The anemia in patients with rHuEPO-induced PRCA is much more severe than the anemia in patients with renal failure that prompted the rHuEPO therapy.[2] In addition, most patients with rHuEPO-induced PRCA become permanently transfusion dependent and may be resistant to other rHuEPO products.[2,5,6]

Health Canada is closely monitoring the issue and has requested that the manufacturer conduct, and submit the results of, further investigations to determine the factors that may have contributed to the increased number of PRCA cases in Canada. More data from ongoing investigations are still required to assess the risks associated with rHuEPO use. Until then, patients receiving rHuEPO should be advised to promptly report to their physician any symptoms associated with worsening anemia (e.g., excessive fatigue, pallor, syncope). Physicians should consult

### Newsletter and Advisories by email

***To receive*** the Newsletter and Advisories ***free*** by email, join Health Canada's ***Health_Prod_Info*** mailing list. ***Go to www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adr.html*** and ***click "subscribe"***.

M121

IMPORTANT NOTE CONCERNING THE FOLLOWING PAGES

THE PAGES WHICH FOLLOW HAVE BEEN FILMED TWICE IN ORDER TO OBTAIN THE BEST REPRODUCTIVE QUALITY

USERS SHOULD CONSULT ALL THE PAGES REPRODUCED ON THE FICHE IN ORDER TO OBTAIN A COMPLETE READING OF THE TEXT.

---

REMARQUE IMPORTANTE CONCERNANT LES PAGES QUI SUIVENT

LES PAGES SUIVANTES ONT ÉTÉ REPRODUITES EN DOUBLE AFIN D'AMÉLIORER LA QUALITÉ DE REPRODUCTION

LES UTILISATEURS DOIVENT CONSULTER TOUTES LES PAGES REPRODUITES SUR LA FICHE AFIN D'OBTENIR LA LECTURE DU TEXTE INTÉGRAL

Micromedia
ProQuest

789 East Eisenhower Parkway
PO Box 1346
Ann Arbor, MI 48106-1346 USA
toll free: 1-800-521-0600
fax: (734) 997-4247
web: www.micromedia.ca

Health Canada Santé Canada

Canada

# Canadian Adverse Reaction Newsletter

Volume 12 • Issue 3 • July 2002

www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html

## In this Issue

Pure red cell aplasia and Eprex 1
Glitazones: update on adverse reactions 2
Safety of human insulins 3
Case presentation: Kava 3
Summary of advisories 4

## Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

## Reporting Adverse Reactions

**Contact Health Canada or a Regional AR Centre free of charge**

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

**Form available at:**

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

## Pure red cell aplasia: suspected association with epoetin alfa (Eprex)

Eprex, a recombinant human erythropoietin (rHuEPO), is indicated for "the treatment of anaemia associated with chronic renal failure (CRF), cancer or concomitantly administered cancer chemotherapy, zidovudine-treated/HIV-infected patients, for use in patients undergoing autologous donation, and to reduce allogenic blood exposure for patients undergoing elective surgery."[1] The "primary adverse effect of erythropoietin has been an excessive increase in the hematocrit following overtreatment with the hormone in patients undergoing hemodialysis, leading to the aggravation of hypertension or thrombotic complications."[1] Recently, however, pure red-cell aplasia (PRCA), a selective failure of the erythroid elements in bone marrow resulting in a normochromic, normocytic anemia, has been reported to be associated with the use of rHuEPO.[2-5] On Nov. 26, 2001, following discussion with Health Canada, the sponsor issued a Dear Healthcare Professional Letter informing physicians of the occurrence of PRCA associated with the use of Eprex.[6] Since then, there has been a marked increase in the number of PRCA cases reported to Health Canada: 21 of the 28 cases reported as of Apr. 10, 2002, were received after the letter was issued.

The mechanism underlying PRCA is not well understood. Autoantibodies against erythropoietin have been shown to inhibit the formation of erythroid colonies by normal bone marrow cells.[3] PRCA has been demonstrated to be induced by drugs and chemicals (e.g., phenytoin, chlorpropamide).[2,5,7] It has also been associated with a variety of conditions including thymomas, lymphoproliferative disorders and viral infections such as hepatitis B and parvovirus infection.[2,7] Although rare, PRCA can occur during the course of renal failure.[2,7] The anemia in patients with rHuEPO-induced PRCA is much more severe than the anemia in patients with renal failure that prompted the rHuEPO therapy.[2] In addition, most patients with rHuEPO-induced PRCA become permanently transfusion dependent and may be resistant to other rHuEPO products.[2,5,6]

Health Canada is closely monitoring the issue and has requested that the manufacturer conduct, and submit the results of, further investigations to determine the factors that may have contributed to the increased number of PRCA cases in Canada. More data from ongoing investigations are still required to assess the risks associated with rHuEPO use. Until then, patients receiving rHuEPO should be advised to promptly report to their physician any symptoms associated with worsening anemia (e.g., excessive fatigue, pallor, syncope). Physicians should consult

### Newsletter and Advisories by email

***To receive*** the Newsletter and Advisories ***free*** by email, join Health Canada's *Health_Prod_Info* mailing list. ***Go to*** *www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adr.html* and ***click*** "*subscribe*".

2008-02532/

the product monograph for hematology monitoring requirements. Health professionals are encouraged to continue to report to Health Canada any suspected or confirmed cases of PRCA in patients using rHuEPO.

Xuguang Li, MD, Ph.D; Supriya Sharma, MD, MPH, FRCPC, Health Canada

## References


1. *Eprex, sterile solution* [product monograph]. Toronto: Janssen-Ortho Inc; 2001 Jan 26.
2. Bunn HF. Drug-induced autoimmune red-cell aplasia. *N Engl J Med* 2002;346(7):522-3.
3. Peces R, de la Torre M, Alcazar R, Urra JM. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996;335(7):523-4.
4. Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997;47(5):331-5.
5. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346(7):469-75.
6. *Important new safety information — Eprex (epoetin alfa): reports of pure red blood cell anemia* [Dear Healthcare Professional Letter]. Toronto: Janssen-Ortho Inc., Ortho Biotech; 2001 Nov 26. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/ztfiles/english/advisory/industry/eprex_e.html (accessed 2002 May 24).
7. Croisille L, Tchernia G, Casadevall N. Autoimmune disorders of erythropoiesis. *Curr Opin Hematol* 2001;8(2):68-73.


# Rosiglitazone (Avandia) and pioglitazone (Actos): update on cardiovascular and hepatic adverse reactions

Rosiglitazone (Avandia) and pioglitazone (Actos), members of the thiazolidinedione oral antidiabetic class of drugs, were marketed in Canada in March and August 2000, respectively. In Canada, Avandia is indicated for use as an adjunct to diet and exercise as monotherapy or in combination with metformin or a sulfonylurea in patients with type 2 diabetes mellitus.[1] Actos is indicated as monotherapy for type 2 diabetes not controlled by diet and exercise.[2]

Health Canada continues to monitor cardiac disorders and hepatic reactions with these drugs. Table 1 summarizes reports of suspected adverse reactions (ARs) associated with rosiglitazone and pioglitazone received since the date they were marketed in Canada to Mar. 1, 2002. Spontaneous reporting systems are suitable to detect signals of potential drug safety issues; however, quantitative comparisons of drug safety cannot be made from these data.

Thirty-six of the 282 reports received for rosiglitazone and 4 of the 29 received for pioglitazone were of heart failure or congestive heart failure. Cases of edema were also reported without heart failure.

Ten of the 282 suspected AR reports received for rosiglitazone indicated a fatal outcome; 3 of these were described in the July 2001 issue of the newsletter.[3] Three of the remaining 7 suspected fatal cases reported heart failure or congestive heart failure, with 2 of these also indicating myocardial infarction. The other 4 fatal cases involved pulmonary edema (1), enlarged abdomen and peripheral edema (1), bone marrow depression with concomitant use of Imuran (1) and a complex case of a serum-sickness-type reaction and erythema multiforme (1), which occurred shortly after the rosiglitazone was started and which resulted in multiple organ failure. There was 1 report of a fatal outcome associated with pioglitazone in which the patient had a cardiorespiratory arrest, was found to have elevated liver enzymes and died of anoxic encephalopathy. The patient had no history of liver disease but had a history of extensive alcohol consumption and was taking other drugs. Causality assessment is difficult in most of these cases because of the lack of information or the complexity of the cases.

People with type 2 diabetes are at increased risk of diabetes-related complications such as congestive heart failure. However, results of an observational study based on analysis of insurance claims indicated that the use of glitazones was associated with a significant increase in risk of heart failure in diabetic patients treated with glitazones compared with diabetic patients who did not use glitazones.[4] However, these results were published as an abstract only, and further research is needed to confirm these findings.

To minimize the risk of hepatic and cardiovascular adverse events, physicians are advised to adhere to all recommendations and monitoring guidance listed in the product

**Table 1: Reports submitted to Health Canada of suspected adverse reactions (ARs) associated with thiazolidinediones from date marketed in Canada to Mar. 1, 2002***

| Variable | Rosiglitazone (Avandia) | Pioglitazone (Actos) |
|---|---|---|
| Date marketed in Canada | March 2000 | August 2000 |
| Total no. of AR reports | 282 | 29 |
| No. of serious reports | 134 | 24 |
| No. of reports with cardiovascular disorders† | 60 | 8 |
| No. of reports with liver and biliary disorders† | 16 | 1 |
| No. of reports with fatal outcome† | 10 | 1 |

*These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products, because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†These reports are a subset of the total AR reports and are represented only once in the most significant category.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

monograph. The product monographs of Avandia[1] and Actos[2] list the following as contraindications:

- known hypersensitivity to the product or any of its components;
- serious hepatic impairment; and
- acute heart failure.

Health Canada has been continuously monitoring the safety profile of the glitazones. The following actions have been taken to inform health care professionals and the public regarding safety issues with these products:

- At product launch in Canada, Dear Healthcare Professional Letters were issued by the manufacturers of Avandia[5] and Actos[6] recommending that precautions be taken and that patients be monitored for liver and cardiac adverse reactions.
- A summary of hepatic, cardiac and hematological reactions with rosiglitazone was presented in the July 2001 issue of the newsletter.[3]
- In consultation with Health Canada a second Dear Healthcare Professional Letter was issued by the manufacturer of Actos (on Nov. 6, 2001[7]) and by the manufacturer of Avandia (on Nov. 13, 2001[8]) regarding new safety information related to fluid retention and congestive heart failure.
- Health Canada issued a public Advisory on the safety profile of the thiazolidinediones on Nov. 29, 2001,[9] related to fluid retention and congestive heart failure.

Your continued reporting of suspected ARs associated with the use of the glitazones is an important factor in evaluating their safety in the postmarketing phase.

Duc Vu, MSc, Ph.D; Mano Murty, MD, CCFP, FCFP; Marielle McMorran, BScPharm, Health Canada

## References


1. *Avandia, rosiglitazone maleate tablets* [product monograph]. Mississauga (ON): GlaxoSmithKline Inc; 2001 Oct 19.
2. *Actos, pioglitazone hydrochloride tablets* [product monograph]. Toronto (ON): Eli Lilly Canada Inc; 2001 Nov 19 / Oct 26.
3. McMorran M, Vu D. Rosiglitazone (Avandia): hepatic, cardiac and hematological reactions. *Can Adverse Drug Reaction Newsl* 2001;11(3):2-3. Also in *CMAJ* 2001;165(1):82-3.
4. Delea T, Hagiwara M, Edelsberg J, Oster G. Exposure to glitazone antidiabetics and risk of heart failure among persons with type 2 diabetes: a retrospective population-based cohort analysis [abstract]. *J Am Coll Cardiol* 2002;39(5 Suppl A):858.
5. *Avandia* [Dear Healthcare Professional Letter]. Oakville (ON): SmithKline Beecham Pharma; March 2000.
6. *Actos* [Dear Healthcare Professional Letter]. Toronto: Eli Lilly Canada Inc; Sept 2000.
7. *Important safety information regarding Actos* [Dear Healthcare Professional Letter]. Toronto: Eli Lilly Canada Inc; 2001 Nov 6. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/actos_e.html (accessed 2002 May 28).
8. *Important safety information regarding Avandia* [Dear Healthcare Professional Letter]. Mississauga (ON): GlaxoSmithKline Inc; 2001 Nov 13. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/avandia_e.html (accessed 2002 May 28).
9. *Important safety reminder for patients taking oral diabetes drugs of the glitazone class, Avandia® and Actos®* [Public Advisory]. Ottawa: Health Canada; 2001 Nov 29. Available: www.hc-sc.gc.ca/english/protection/warnings/2001/2001_132e.htm (accessed 2002 May 28).


## "It's Your Health": The Safety of Human Insulins

In the previous 2 years attention has been focused, in media reports and elsewhere, on concerns regarding the safety of recombinant human insulin and the availability of animal insulin in Canada. In an effort to clarify these issues Health Canada has posted an "It's Your Health" document on its Web site (www.hc-sc.gc.ca/english/iyh/insulins.html), with a link to it from the Canadian Diabetes Association's update on human and animal insulins (www.diabetes.ca/Section_About/bromley.asp). A distribution by fax to targeted health professionals and special interest groups was also done.

The document briefly outlines the background of the manufacture and sale of recombinant human and animal insulins in Canada, and their availability. In addition, it addresses the benefits of human insulins, how Health Canada monitors the adverse effects of insulin, and the effects of switching insulins, stressing that the choice of insulin for an individual should be made after discussion with the treating physician.

From 1983 to Mar. 31, 2002, Health Canada received about 550 reports of suspected ARs associated with recombinant human insulins. Of these suspected AR reports, 9 indicated a fatal outcome. From 1965, when Health Canada started monitoring ARs, until Mar. 31, 2002, about 250 reports of ARs associated with animal insulins were received, 20 of which

## Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

### Kava

**As a result of the Public Advisory concerning kava and liver toxicity issued by Health Canada on Jan. 16, 2002, 3 case reports of suspected hepatic adverse reactions were received. One of these cases involved a 53-year-old woman who took 3 to 10 capsules of kava (dosage unspecified) daily over a 2-year period. She also took St. John's wort, vitamins and other herbs for depression and anxiety. Four years earlier the patient had developed an inflamed liver because of alcohol consumption but had stopped drinking in the last 2 years. Three weeks before medical consultation, the patient experienced fatigue, vomiting, loss of weight, jaundice and darker urine. At presentation she had an enlarged liver and elevated bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels. After the patient stopped taking the kava, her liver profile returned to normal and her symptoms resolved.**

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

2008-02532/

the product monograph for hematology monitoring requirements. Health professionals are encouraged to continue to report to Health Canada any suspected or confirmed cases of PRCA in patients using rHuEPO.

Xuguang Li, MD, Ph.D; Supriya Sharma, MD, MPH, FRCPC, Health Canada

## References


1. *Eprex, sterile solution* [product monograph]. Toronto: Janssen-Ortho Inc; 2001 Jan 26.
2. Bunn HF. Drug-induced autoimmune red-cell aplasia. *N Engl J Med* 2002;346(7):522-3.
3. Peces R, de la Torre M, Alcazar R, Urra JM. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996;335(7):523-4.
4. Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997;47(5):331-5.
5. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346(7):469-75.
6. *Important new safety information — Eprex [epoetin alfa]: reports of pure red blood cell anemia* [Dear Healthcare Professional Letter]. Toronto: Janssen-Ortho Inc., Ortho Biotech; 2001 Nov 26. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex_e.html (accessed 2002 May 24).
7. Crouzille L, Tchernia G, Casadevall N. Autoimmune disorders of erythropoiesis. *Curr Opin Hematol* 2001;8(2):68-73.


# Rosiglitazone (Avandia) and pioglitazone (Actos): update on cardiovascular and hepatic adverse reactions

Rosiglitazone (Avandia) and pioglitazone (Actos), members of the thiazolidinedione oral antidiabetic class of drugs, were marketed in Canada in March and August 2000, respectively. In Canada, Avandia is indicated for use as an adjunct to diet and exercise as monotherapy or in combination with metformin or a sulfonylurea in patients with type 2 diabetes mellitus.[1] Actos is indicated as monotherapy for type 2 diabetes not controlled by diet and exercise.[2]

Health Canada continues to monitor cardiac disorders and hepatic reactions with these drugs. Table 1 summarizes reports of suspected adverse reactions (ARs) associated with rosiglitazone and pioglitazone received since the date they were marketed in Canada to Mar. 1, 2002. Spontaneous reporting systems are suitable to detect signals of potential drug safety issues; however, quantitative comparisons of drug safety cannot be made from these data.

Thirty-six of the 282 reports received for rosiglitazone and 4 of the 29 received for pioglitazone were of heart failure or congestive heart failure. Cases of edema were also reported without heart failure.

Ten of the 282 suspected AR reports received for rosiglitazone indicated a fatal outcome; 3 of these were described in the July 2001 issue of the newsletter.[3] Three of the remaining 7 suspected fatal cases reported heart failure or congestive heart failure, with 2 of these also indicating myocardial infarction. The other 4 fatal cases involved pulmonary edema (1), enlarged abdomen and peripheral edema (1), bone marrow depression with concomitant use of Imuran (1) and a complex case of a serum-sickness-type reaction and erythema multiforme (1), which occurred shortly after the rosiglitazone was started and which resulted in multiple organ failure. There was 1 report of a fatal outcome associated with pioglitazone in which the patient had a cardiorespiratory arrest, was found to have elevated liver enzymes and died of anoxic encephalopathy. The patient had no history of liver disease but had a history of extensive alcohol consumption and was taking other drugs. Causality assessment is difficult in most of these cases because of the lack of information or the complexity of the cases.

People with type 2 diabetes are at increased risk of diabetes-related complications such as congestive heart failure. However, results of an observational study based on analysis of insurance claims indicated that the use of glitazones was associated with a significant increase in risk of heart failure in diabetic patients treated with glitazones compared with diabetic patients who did not use glitazones.[4] However, these results were published as an abstract only, and further research is needed to confirm these findings.

To minimize the risk of hepatic and cardiovascular adverse events, physicians are advised to adhere to all recommendations and monitoring guidance listed in the product

**Table 1: Reports submitted to Health Canada of suspected adverse reactions (ARs) associated with thiazolidinediones from date marketed in Canada to Mar. 1, 2002***

| Variable | Rosiglitazone (Avandia) | Pioglitazone (Actos) |
|---|---|---|
| Date marketed in Canada | March 2000 | August 2000 |
| Total no. of AR reports | 282 | 29 |
| No. of serious reports | 134 | 24 |
| No. of reports with cardiovascular disorders† | 60 | 8 |
| No. of reports with liver and biliary disorders† | 16 | 1 |
| No. of reports with fatal outcome† | 10 | 1 |

*These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products, because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†These reports are a subset of the total AR reports and are represented only once in the most significant category.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

monograph. The product monographs of Avandia[1] and Actos[2] list the following as contraindications:

- known hypersensitivity to the product or any of its components;
- serious hepatic impairment; and
- acute heart failure.

Health Canada has been continuously monitoring the safety profile of the glitazones. The following actions have been taken to inform health care professionals and the public regarding safety issues with these products:

- At product launch in Canada, Dear Healthcare Professional Letters were issued by the manufacturers of Avandia[5] and Actos[6] recommending that precautions be taken and that patients be monitored for liver and cardiac adverse reactions.
- A summary of hepatic, cardiac and hematological reactions with rosiglitazone was presented in the July 2001 issue of the newsletter.[7]
- In consultation with Health Canada a second Dear Healthcare Professional Letter was issued by the manufacturer of Actos (on Nov. 6, 2001[7]) and by the manufacturer of Avandia (on Nov. 13, 2001[8]) regarding new safety information related to fluid retention and congestive heart failure.
- Health Canada issued a public Advisory on the safety profile of the thiazolidinediones on Nov. 29, 2001,[9] related to fluid retention and congestive heart failure.

Your continued reporting of suspected ARs associated with the use of the glitazones is an important factor in evaluating their safety in the postmarketing phase.

Duc Vu, MSc, Ph.D; Mano Murty, MD, CCFP, FCFP; Marielle McMorran, BScPharm, Health Canada

## References


1. *Avandia, rosiglitazone maleate tablets* [product monograph]. Mississauga (ON): GlaxoSmithKline Inc; 2001 Oct 19.
2. *Actos, pioglitazone hydrochloride tablets* [product monograph]. Toronto (ON): Eli Lilly Canada Inc; 2001 Nov 19 / Oct 26.
3. McMorran M, Vu D. Rosiglitazone (Avandia): hepatic, cardiac and hematological reactions. *Can Adverse Drug Reaction Newsl* 2001;11(3):2-3. Also in *CMAJ* 2001;165(1):82-3.
4. Delea T, Hagiwara M, Edelsberg J, Oster G. Exposure to glitazone antidiabetics and risk of heart failure among persons with type 2 diabetes: a retrospective population-based cohort analysis [abstract]. *J Am Coll Cardiol* 2002;39(5 Suppl A):858.
5. *Avandia* [Dear Healthcare Professional Letter]. Oakville (ON): SmithKline Beecham Pharma; March 2000.
6. *Actos* [Dear Healthcare Professional Letter]. Toronto: Eli Lilly Canada Inc; Sept 2000.
7. *Important safety information regarding Actos* [Dear Healthcare Professional Letter]. Toronto: Eli Lilly Canada Inc; 2001 Nov 6. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/actos_e.html (accessed 2002 May 28).
8. *Important safety information regarding Avandia* [Dear Healthcare Professional Letter]. Mississauga (ON): GlaxoSmithKline Inc; 2001 Nov 13. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/avandia_e.html (accessed 2002 May 28).
9. *Important safety reminder for patients taking oral diabetes drugs of the glitazone class, Avandia® and Actos®* [Public Advisory]. Ottawa: Health Canada; 2001 Nov 29. Available: www.hc-sc.gc.ca/english/protection/warnings/2001/2001_132e.htm (accessed 2002 May 28).


## "It's Your Health": The Safety of Human Insulins

In the previous 2 years attention has been focused, in media reports and elsewhere, on concerns regarding the safety of recombinant human insulin and the availability of animal insulin in Canada. In an effort to clarify these issues Health Canada has posted an "It's Your Health" document on its Web site (www.hc-sc.gc.ca/english/iyh/insulins.html), with a link to it from the Canadian Diabetes Association's update on human and animal insulins (www.diabetes.ca/Section_About/bromley.asp). A distribution by fax to targeted health professionals and special interest groups was also done.

The document briefly outlines the background of the manufacture and sale of recombinant human and animal insulins in Canada, and their availability. In addition, it addresses the benefits of human insulins, how Health Canada monitors the adverse effects of insulin, and the effects of switching insulins, stressing that the choice of insulin for an individual should be made after discussion with the treating physician.

From 1983 to Mar. 31, 2002, Health Canada received about 550 reports of suspected ARs associated with recombinant human insulins. Of these suspected AR reports, 9 indicated a fatal outcome. From 1965, when Health Canada started monitoring ARs, until Mar. 31, 2002, about 250 reports of ARs associated with animal insulins were received, 20 of which

## Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

### Kava

**As a result of the Public Advisory concerning kava and liver toxicity issued by Health Canada on Jan. 16, 2002, 3 case reports of suspected hepatic adverse reactions were received. One of these cases involved a 53-year-old woman who took 3 to 10 capsules of kava (dosage unspecified) daily over a 2-year period. She also took St. John's wort, vitamins and other herbs for depression and anxiety. Four years earlier the patient had developed an inflamed liver because of alcohol consumption but had stopped drinking in the last 2 years. Three weeks before medical consultation, the patient experienced fatigue, vomiting, loss of weight, jaundice and darker urine. At presentation she had an enlarged liver and elevated bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels. After the patient stopped taking the kava, her liver profile returned to normal and her symptoms resolved.**

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

**Summary of health professional and consumer advisories issued since Feb. 15, 2002**

| Date | Product | Subject and Web address |
|---|---|---|
| May 23 | Celebrex (celecoxib) | Important safety information for patients taking CELEBREX® (celecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_40e.htm |
| May 16 | Longdan | Warning not to consume Longdan and Lung Tan Xie Gan Products — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_38e.htm |
| May 16 | Plas+SD | Important Safety Information - PLAS+SD plasma (human) — Precision Pharma Services Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/plas_sd_plasma_e.html |
| May 14 | Rapamune (sirolimus) | Important correction to drug Safety Information on Rapamune www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/rapamune_e.html |
| May 13 | Celebrex (celecoxib) | Important drug safety information on Celebrex www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/celebrex_e.html |
| May 2002 | Insulins | It's Your Health: The safety of human insulins — consumer information www.hc-sc.gc.ca/english/iyh/insulins.html |
| Apr. 29 | HIV test kits | Health Canada advises Canadians about potential false results with certain rapid HIV test kits — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_31e.htm |
| Apr. 19 | Vioxx (rofecoxib) | Important safety information for patients taking VIOXX® (rofecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_29e.htm |
| Apr. 15 | Vioxx (rofecoxib) | Important drug safety information on VIOXX® — Merck Frosst Canada Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/vioxx_e.html |
| Apr. 12 | IGIV (Immune Globulin) | Thrombotic events and immune globulin intravenous (IGIV) — Baxter www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/igiv_e.html |
| Apr. 11 | Tutoplast Dura | Important medical devices safety advisory — Tutoplast Dura manufactured by Tutogen Medical GmbH www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /tpd/tutogen_e.html |
| Apr. 5 | Hua Fo | Health Canada warns public not to use Hua Fo (DIN 02243366) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_26e.htm |
| Apr. 4 | Phosphate Solutions | Important safety information for patients taking sodium phosphates oral solutions (Fleet® Phospho-soda® and Phosphates Solution) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_22e.htm |
| Mar. 27 | Meridia (sibutramine) | Health Canada investigates safety of MERIDIA® (sibutramine) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_21e.htm |
| Mar. 22 | Non-sterile medical devices | Non-sterile medical devices labeled as sterile manufactured by A&A Medical, Rocket USA and LifeQuest www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd /rocket_e.html |
| Mar. 18 | Sodium Phosphates Oral Solutions | Important safety information regarding Phosphates Solution (Sodium Phosphates Oral Solution DIN 02230399) — Pharmascience Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/sodium_phosphates_e.html |
| Mar. 15 | Sodium Phosphates Oral Solutions | Important safety information regarding Fleet® Phospho-Soda® (Sodium Phosphates Oral Solution) — Johnson & Johnson • Merck www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/fleet-phospho-soda_e.html |
| Mar. 6 | Zerit (stavudine, d4T) | Symptoms mimicking the clinical presentation of Guillain–Barré syndrome associated with ZERIT® (stavudine, d4T) — Bristol-Myers Squibb www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/zerit_stavudine_e.html |

***To receive*** the Newsletter and health product Advisories by email, join Health Canada's ***Health_Prod_Info*** mailing list. ***Go to*** **www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adr.html** and ***click "subscribe"***.

were of a fatal outcome. Quantitative safety comparisons of these products cannot be made on the basis of spontaneous AR reports because patient exposure is unknown and underreporting exists.

Recombinant human insulins have an established safety profile, with over 200 000 Canadians using them daily to manage their diabetes. If one assumes that patients have 2 injections a day on average, about 146 million doses are administered per year. Considering the high numbers of users, the complexity of diabetes as a disease and the benefits obtained with the use of human insulins, the number of reports of suspected ARs is not believed to suggest any unusual trend in the safety profile of these products. Regulators in other international jurisdictions have confirmed similar findings.

Supriya Sharma MD, MPH, FRCPC, Health Canada


# Canadian Adverse Reaction Newsletter

**Marketed Health Products Directorate**
AL 0201C2
Ottawa ON K1A 1B9
Tel 613 957-0337
Fax 613 957-0335

**Health professionals/consumers report toll free:**
Tel 866 234-2345
Fax 866 678-6789
Email: cadrmp@hc-sc.gc.ca

**Editors**
Ann Sztuke-Fournier, BPharm
Marielle McMorran, BScPharm

**Acknowledgements**
Expert Advisory Committee on Pharmacovigilance, AR Regional Centres and Health Canada staff

**Suggestions?**
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca


**Copyright**
Her Majesty the Queen in Right of Canada, 2002. This publication may be reproduced without permission provided the source is fully acknowledged. The use of this publication for advertising purposes is prohibited. Health Canada does not assume liability for the accuracy or authenticity of the information submitted in case reports.

ISSN 1499-9447, Cat no H42-4/1-12-3E

USPS periodical postage paid at Champlain, NY, and additional locations.

**Aussi disponible en français**

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

**Summary of health professional and consumer advisories issued since Feb. 15, 2002**

| Date | Product | Subject and Web address |
|---|---|---|
| May 23 | Celebrex (celecoxib) | Important safety information for patients taking CELEBREX® (celecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_40e.htm |
| May 16 | Longdan | Warning not to consume Longdan and Lung Tan Xie Gan Products — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_38e.htm |
| May 16 | Plas+SD | Important Safety Information - PLAS+SD plasma (human) — Precision Pharma Services Inc www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/plas_sd_plasma_e.html |
| May 14 | Rapamune (sirolimus) | Important correction to drug Safety Information on Rapamune www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/rapamune_e.html |
| May 13 | Celebrex (celecoxib) | Important drug safety information on Celebrex www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/celebrex_e.html |
| May 2002 | Insulins | It's Your Health: The safety of human insulins — consumer information www.hc-sc.gc.ca/english/iyh/insulins.html |
| Apr. 29 | HIV test kits | Health Canada advises Canadians about potential false results with certain rapid HIV test kits — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_31e.htm |
| Apr. 19 | Vioxx (rofecoxib) | Important safety information for patients taking VIOXX® (rofecoxib) — consumer Information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_29e.htm |
| Apr. 15 | Vioxx (rofecoxib) | Important drug safety information on VIOXX® — Merck Frosst Canada Inc www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/vioxx_e.html |
| Apr. 12 | IGIV (Immune Globulin) | Thrombotic events and immune globulin intravenous (IGIV) — Baxter www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/igiv_e.html |
| Apr. 11 | Tutoplast Dura | Important medical devices safety advisory — Tutoplast Dura manufactured by Tutogen Medical GmbH www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /tpd/tutogen_e.html |
| Apr. 5 | Hua Fo | Health Canada warns public not to use Hua Fo (DIN 02243366) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_26e.htm |
| Apr. 4 | Phosphate Solutions | Important safety information for patients taking sodium phosphates oral solutions (Fleet® Phospho-soda® and Phosphates Solution) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_22e.htm |
| Mar. 27 | Meridia (sibutramine) | Health Canada investigates safety of MERIDIA® (sibutramine) — consumer information www.hc-sc.gc.ca/english/protection/warnings/2002/2002_21e.htm |
| Mar. 22 | Non-sterile medical devices | Non-sterile medical devices labeled as sterile manufactured by A&A Medical, Rocket USA and LifeQuest www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd /rocket_e.html |
| Mar. 18 | Sodium Phosphates Oral Solutions | Important safety information regarding Phosphates Solution (Sodium Phosphates Oral Solution DIN 02230399) — Pharmascience Inc. www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/sodium_phosphates_e.html |
| Mar. 15 | Sodium Phosphates Oral Solutions | Important safety information regarding Fleet® Phospho-Soda® (Sodium Phosphates Oral Solution) — Johnson & Johnson • Merck www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/fleet-phospho-soda_e.html |
| Mar. 6 | Zerit (stavudine, d4T) | Symptoms mimicking the clinical presentation of Guillain-Barré syndrome associated with ZERIT® (stavudine, d4T) — Bristol-Myers Squibb www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory /industry/zerit_stavudine_e.html |

***To receive*** the Newsletter and health product Advisories by email, join Health Canada's ***Health_Prod_Info*** mailing list. ***Go to*** **www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adr.html** and ***click "subscribe"***

were of a fatal outcome. Quantitative safety comparisons of these products cannot be made on the basis of spontaneous AR reports because patient exposure is unknown and underreporting exists.

Recombinant human insulins have an established safety profile, with over 200 000 Canadians using them daily to manage their diabetes. If one assumes that patients have 2 injections a day on average, about 146 million doses are administered per year. Considering the high numbers of users, the complexity of diabetes as a disease and the benefits obtained with the use of human insulins, the number of reports of suspected ARs is not believed to suggest any unusual trend in the safety profile of these products. Regulators in other international jurisdictions have confirmed similar findings.

Supriya Sharma MD, MPH, FRCPC, Health Canada


# Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0201C2
Ottawa ON K1A 1B9
Tel 613 957-0337
Fax 613 957-0335

**Health professionals/consumers report toll free:**
Tel 866 234-2345
Fax 866 678-6789
Email: cadrmp@hc-sc.gc.ca

**Editors**
Ann Szbuke-Fournier, BPharm
Marielle McMorran, BScPharm

**Acknowledgements**
Expert Advisory Committee on Pharmacovigilance, AR Regional Centres and Health Canada staff

**Suggestions?**
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca


**Copyright**
Her Majesty the Queen in Right of Canada, 2002. This publication may be reproduced without permission provided the source is fully acknowledged. The use of this publication for advertising purposes is prohibited. Health Canada does not assume liability for the accuracy or authenticity of the information submitted in case reports.

ISSN 1499-9447, Cat no H42-4/1-12-3E

USPS periodical postage paid at Champlain, NY, and additional locations.

**Aussi disponible en français**

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.